(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 April 2001 (26.04.2001)

PCT

(10) International Publication Number
WO 01/29010 A1

(51) International Patent Classification[7]: C07D 239/545, A61K 31/513

(21) International Application Number: PCT/US00/28809

(22) International Filing Date: 18 October 2000 (18.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/160,821 21 October 1999 (21.10.1999) US

(71) Applicant (*for all designated States except US*): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): ALI, Amjad [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). TAYLOR, Gayle, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). GRAHAM, Donald, W. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

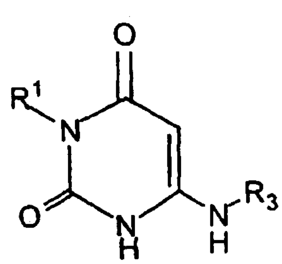
(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: GRAM-POSITIVE SELECTIVE ANTIBACTERIAL COMPOUNDS, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT



(I)

(57) Abstract: The compounds of formula (I) including pharmaceutically acceptable salts, stereoisomers or esters thereof are disclosed.

WO 01/29010 A1

TITLE OF THE INVENTION

GRAM-POSITIVE SELECTIVE ANTIBACTERIAL COMPOUNDS, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT

BACKGROUND OF THE INVENTION

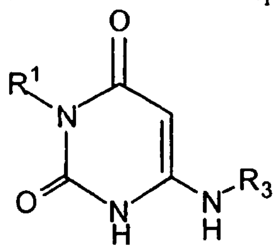
DNA polymerase III (DNA pol III) enzyme has been shown to be crucial in the replicative DNA synthesis of Gram-positive bacteria. Since DNA pol III shows little homology to mammalian or gram-negative bacterial DNA polymerases it represents an attractive target for inhibition in the discovery of new Gram-positive selective antibacterial agents.

G.E. Wright et al., *J. Med. Chem* **1974**, 12, 1277-1282; **1977**, 20, 1181-1185; **1980**, 23, 34-38;and **1984**, 27, 181-185; *Pharmac. Ther.* **1990**, 47, 447-497; and *Nucleic acids research* **1990**, 24, 7381 have reported on a series of guanine and uracil based DNA pol III inhibitors. See also WO 96/06614. Inhibitory action of these compounds is reversed by specific purine deoxyribonucleoside 5'-triphosphates, dGTP in the case of uracil derivatives and dATP in the case of isocytosines. Enzyme inhibition results directly from the immobilization of pol III in a ternary complex composed of the DNA template, the inhibitor and the enzyme (see, e.g., G. Wright, et al., *J. Med. Chem* **1974**, 12, 1277-1282). However, these compounds are insoluble and contain unsuitable functionalities and therefore unattractive.

The present invention relates to DNA polymerase III inhibitors which are useful against gram positive microorganisms, especially methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant *Staphylococcus epidermidis* (MRSE), *B. subtilis*, *Enterococcus fecalis/fecium*, *Streptococus pneumoniae* and methicillin resistant coagulase negative *Staphylococci* (MRCNS). The compounds represent a novel class of DNA pol III inhibitors which have advantages with respect to efficacy, toxicity and/or metabolism. The antibacterial compounds of the present invention thus comprise an important contribution to therapy for treating infections caused by these difficult to control pathogens. There is an increasing need for agents effective against such pathogens (MRSA/MRCNS) which are at the same time relatively free from undesirable side effects.

SUMMARY OF THE INVENTION

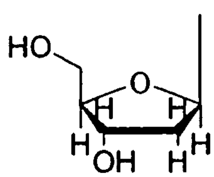
The compounds of the invention are represented by formula I:



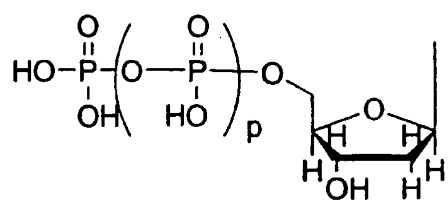
I

including pharmaceutically acceptable salts, stereoisomers or esters thereof, wherein:

R^1 represents H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $(CH_2)_nC_{3-10}$ alicyclic, $(CH_2)_nC_{3-10}$ heterocyclic, $(CH_2)_nC_{5-10}$ aryl, $(CH_2)_nC_{5-10}$heteroaryl, $(CH_2)_n$diaryl, $(CH_2)_nOR^2$, $(CH_2)_mCO_2R^2$, $(CH_2)_nN(R^2)_2$, $(CH_2)_nCON(R^2)_2$,



, or



;

said alkyl, alkenyl, alkynyl, aryl, heteroaryl, optionally substituted with 1 to 3 groups of R^a; and providing that when R^1 is H, CH_3, CH_2CH_3, $CH_2CH{=}CH_2$ or $(CH_2)_{2-5}CH_3$, R3 cannot be 3,4-trimethyleneanilino or when R^1 is H, CH_3, CH_2CH_3, $CH_2CH{=}CH_2$ or $(CH_2)_{2-5}CH_3$, R3 cannot be 3-ethyl-4-methylanilino;

m is 0 to 5; n is 0 to 5; p is 0 to 2;

R^2 represents H, C_{1-10} alkyl;

R^3 is C_{3-10}alicyclic, C_{3-10}heterocyclic, $(CH_2)_nC_{5-10}$aryl, $(CH_2)_nC_{5-10}$ heteroaryl, $NH(CH_2)_nC_{5-10}$aryl, or $NH(CH_2)_nC_{5-10}$heteroaryl, said aryl or heteroaryl optionally substituted with 1 to 3 groups of R;

R is H, C_{1-6} alkyl, C_{1-6} alkyl-OH, halo, C_{1-6} alkylhalo, OR^2, CN, CF_3, $N(R^2)_2$, CO_2R^2, NO_2, $NHCOR^2$, SO_2R^2 or SR^2;

R^a represents C_{1-10} alkyl, C_{3-8} cycloalkyl, halo, C_{1-6} alkyl-OH, OH, C_{1-6} alkylhalo, CF_3, NH_2, C_{1-6} alkylNH_2, -SH, -SC_{1-4}alkyl, -CN, -COC_{1-8}alkyl, -C_{5-10} aryl, -COC_{5-10} aryl, -C_{5-10} heteroaryl, -COC_{5-10} heteroaryl, C_{1-4}alkyl-aryl, $CONR^6R^7$, $NHCOR^2$, $OCOR^6$, -$NR^6(CO)R^7$, $NR^6(CO)NHR^7$, $NHSO_2R^6$, OR^6, CO_2R^6, or NR^6R^7 and

R^6 & R^7 independently represent H, C_{1-8} alkyl, C_{3-8} cycloalkyl, or -C_{5-10} aryl.

DETAILED DESCRIPTION OF THE INVENTION

The invention is described herein in detail using the terms defined below unless otherwise specified.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight or branched, saturated or unsaturated. Preferred alkyl groups include methyl, ethyl, propyl, hexyl, isopropyl, butyl and t-butyl. When substituted, alkyl groups may be substituted with up to 3 substituent groups, selected from R^a as defined, at any available point of attachment. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group".

Cycloalkyl is a specie of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings which are fused. Preferred cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. When substituted, cycloalkyl groups may be substituted with up to 3 substituents selected from R^a as defined.

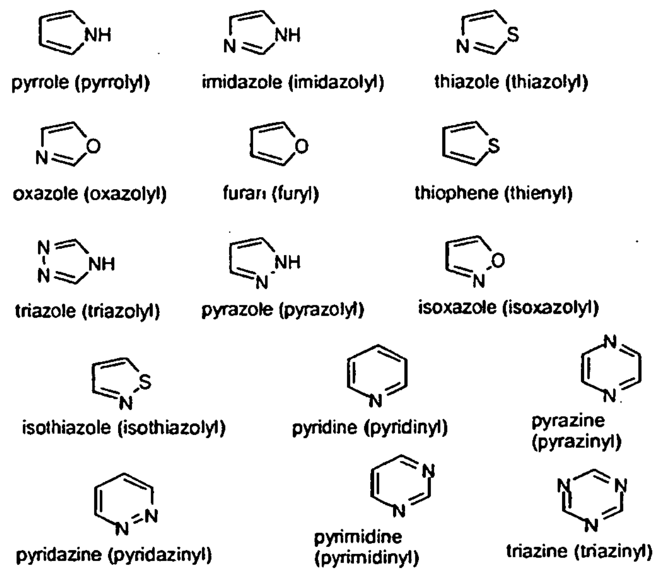
The term unsaturated alkyl refers to "alkenyl" or "alkynyl". The term "alkenyl" refers to an unsaturated alkyl such as a hydrocarbon radical, straight or branched containing from 2 to 6 carbon atoms and at least one carbon to carbon double bond. Preferred alkenyl groups include propenyl, hexenyl and butenyl. The term "alkynyl" refers to an unsaturated alkyl such as a hydrocarbon radical straight or branched, containing from 2 to 16 carbon atoms and at least one carbon to carbon triple bond. Preferred alkynyl groups include propynyl, hexenyl and butynyl.

The term "alicyclic" refers to non-aromatic monocyclic or bicyclic C_3-C_{10} hydrocarbons, including unsaturated, which can be substituted with 0-3 groups of R. Examples of said groups include cycloalkyls such as cyclohexyl, cyclopentyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]hepta-2,5-dienyl, bicyclo[2.2.2]octyl, bicyclo[2.2.2]octa-2,5-dienyl.

The term "heterocyclic" refers to a monocyclic non-aromatic moiety containing 3-8 ring atoms or a bicyclic non-aromatic moiety containing 6-10 ring atoms, at least one of which ring atoms is a heteroatom selected from nitrogen, oxygen and sulfur and where one additional ring atom may be oxygen or sulfur. Examples of heterocyclic groups are furanyl, pyranyl, morpholinyl, dioxanyl and quinuclidinyl.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and the like, as well as rings which are fused, e.g., naphthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl, naphthyl and phenanthrenyl. Aryl groups may likewise be substituted as defined. Preferred substituted aryls include phenyl and naphthyl.

The term "heteroaryl" (Het) refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one or two additional carbon atoms is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms, said heteroaryl group being optionally substituted as described herein. Examples of this type are pyrrole, pyridine, oxazole, thiazole benzimidazolyl, and oxazine. Additional nitrogen atoms may be present together with the first nitrogen and oxygen or sulfur, giving, e.g., thiadiazole. Heteroaryl groups may likewise be substituted with 1 to 3 groups of R^a as defined. Examples include the following:



The term "heteroatom" means O, S or N, selected on an independent basis.

Halogen and "halo" refer to bromine, chlorine, fluorine and iodine.

When a group is termed "substituted", unless otherwise indicated, this means that the group contains from 1 to 3 substituents thereon.

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T. W. et al. Protective Groups in Organic Synthesis Wiley, New York (1991). Examples of suitable protecting groups are contained throughout the specification.

Some of the compounds of the present invention may be protected by protecting groups. Conventional protecting groups consist of groups which are used to protectively block the hydroxyl or carboxyl group during the synthesis procedures described herein. These conventional blocking groups are readily removable, i.e., they can be removed, if desired, by procedures which will not cause cleavage or other disruption of the remaining portions of the molecule. Such procedures include chemical and enzymatic hydrolysis, treatment with chemical reducing or oxidizing agents under mild conditions, treatment with a transition metal catalyst and a nucleophile and catalytic hydrogenation.

Examples of carboxyl protecting groups include allyl, benzhydryl, 2-naphthylmethyl, benzyl, silyl such as t-butyldimethylsilyl (TBDMS), phenacyl, p-methoxybenzyl, o-nitrobenzyl, p-methoxyphenyl, p-nitrobenzyl, 4-pyridylmethyl and t-butyl.

Examples of suitable hydroxy protecting groups include triethylsilyl, t-butyldimethylsilyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, benzyloxycarbonyl, allyloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl and the like.

The compounds of the present invention are useful per se and in their pharmaceutically acceptable salt and ester forms for the treatment of bacterial infections in animal and human subjects. The term "pharmaceutically acceptable ester, salt or hydrate," refers to those salts, esters and hydrated forms of the compounds of the present invention which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which may favorably affect the pharmacokinetic properties of said compounds, such as palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, solubility, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers. Thus, the present invention is also concerned with pharmaceutical compositions and methods of treating bacterial infections utilizing as an active ingredient the novel carbapenem compounds.

The pharmaceutically acceptable salts referred to above may take the form of a negative charge, which is balanced by a counterion, e.g., an alkali metal cation such as sodium or potassium. Other pharmaceutically acceptable counterions may be calcium, magnesium, zinc, ammonium, or alkylammonium cations such as tetramethylammonium, tetrabutylammonium, choline, triethylhydroammonium, meglumine, triethanolhydroammonium, etc.

The pharmaceutically acceptable salts referred to above also include acid addition salts. Thus, the Formula I compounds can be used in the form of salts derived from inorganic or organic acids. Included among such salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate,

dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

Acid addition salts of the compounds of formula I include compounds that contain a protonated, basic moiety. Compounds containing a basic moiety are capable of protonation in aqueous media near pH 7, so that the basic moiety can exist as an equilibrium mixture of its neutral form and acid addition (protonated) form. The more basic the group, the greater the degree of protonation near pH 7. All such compounds are included in the present invention.

The pharmaceutically acceptable esters are such as would be readily apparent to a medicinal chemist, and include, for example, those described in detail in U.S. Pat. No. 4,309,438. Included within such pharmaceutically acceptable esters are those which are hydrolyzed under physiological conditions, such as pivaloyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, and others described in detail in U.S. Pat. No. 4,479,947. These are also referred to as "biolabile esters".

Biolabile esters are biologically hydrolizable, and may be suitable for oral administration, due to good absorption through the stomach or intenstinal mucosa, resistance to gastric acid degradation and other factors. Examples of biolabile esters include compounds in which M represents an alkoxyalkyl, alkylcarbonyloxyalkyl, alkoxycarbonyloxyalkyl, cycloalkoxyalkyl, alkenyloxyalkyl, aryloxyalkyl, alkoxyaryl, alkylthioalkyl, cycloalkylthioalkyl, alkenylthioalkyl, arylthioalkyl or alkylthioaryl group. These groups can be substituted in the alkyl or aryl portions thereof with acyl or halo groups. The following M species are examples of biolabile ester forming moieties.: acetoxymethyl, 1-acetoxyethyl, 1-acetoxypropyl, pivaloyloxymethyl, 1-isopropyloxycarbonyloxyethyl, 1-cyclohexyloxycarbonyl-oxyethyl, phthalidyl and (2-oxo-5-methyl-1,3-dioxolen-4-yl)methyl.

A subset of compounds of formula I which is of interest relates to those compounds where R^1 represents C_{1-8} alkyl, C_{2-8} alkenyl, $(CH_2)_nC_{5-10}$ aryl, or $(CH_2)_nC_{5-10}$ alicyclic, said alkyl, alkenyl, aryl or alicyclic optionally substituted with 1-3 groups of R^a. Within this subset, all other variables are as originally defined.

Another subset of compounds of formula I which is of interest relates to those compounds where R^3 is C_{3-10}alicyclic, $(CH_2)_nC_{5-10}$aryl, $(CH_2)_nC_{5-10}$heteroaryl, or $NH(CH_2)_nC_{5-10}$aryl, said aryl or heteroaryl optionally substituted with 1 to 3 groups of R. Within this subset, all other variables are as originally defined.

A preferred subset of compounds of formula I that is of interest relates to compounds where R^1 represents C_{1-8} alkyl, C_{2-8} alkenyl, $(CH_2)_nC_{5-10}$ aryl, or $(CH_2)_nC_{5-10}$ alicyclic, said alkyl, alkenyl, aryl or alicyclic optionally substituted with 1-3 groups of R^a; and R^3 represents C_{3-10}alicyclic, $(CH_2)_nC_{5-10}$aryl, $(CH_2)_nC_{5-10}$heteroaryl, or $NH(CH_2)_nC_{5-10}$aryl, said aryl or heteroaryl optionally substituted with 1 to 3 groups of R, optionally substituted with 1 to 3 groups of R. Within this subset, all other variables are as originally defined.

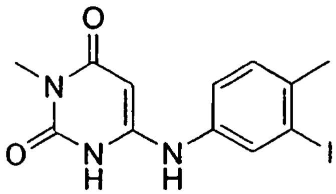
Also included in this invention is a pharmaceutical composition comprised of a compound in accordance with formula I in combination with a pharmaceutically acceptable carrier.

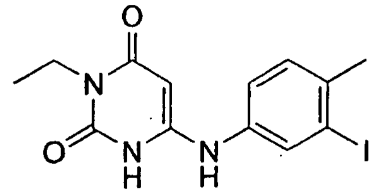
Also included in this invention is a method of treating a bacterial infection comprising administering to a mammalian patient in need of such treatment a compound as defined in claim 1 in an amount which is effective for treating a bacterial infection.

Still included within the scope of this invention is a method of treating a bacterial infection involving methicillin resistant Staphylococcus aureus, methicillin resistant Staphylococcus epidermidis, B. subtilis, Enterococcus facalis/fecium, Streptococcus pneumoniae, methicillin resistant coagulase negative Staphylococci microoganisms or any combination thereof comprising administering to a mammalian patient in need of such treatment a compound of formula I in an amount which is effective for treating a bacterial infection.

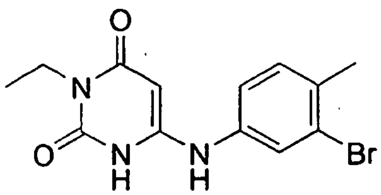
Representative examples of compounds of the invention are found in Table I.

TABLE 1

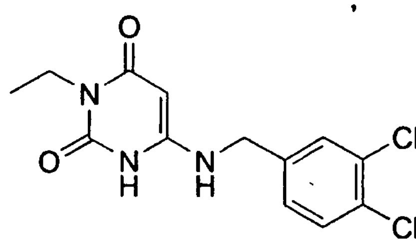




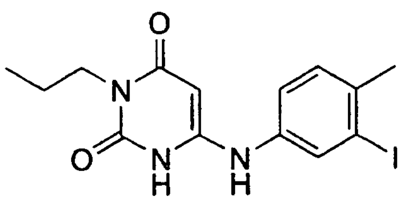
,



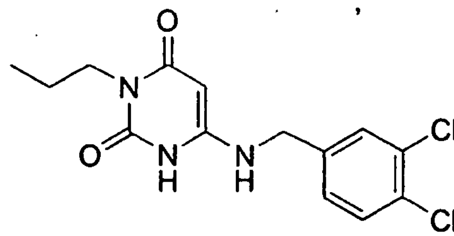
,



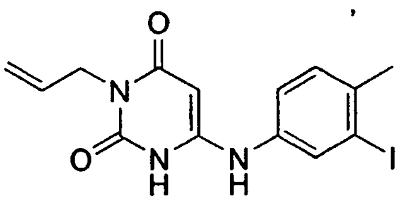
,



,

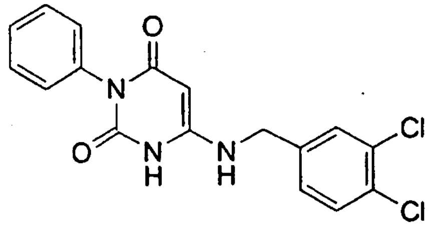
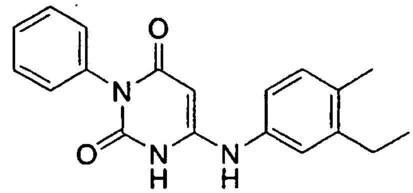


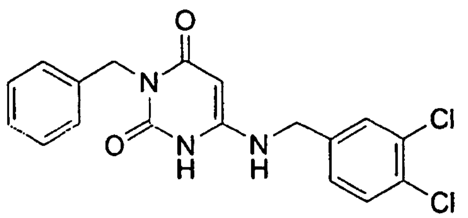
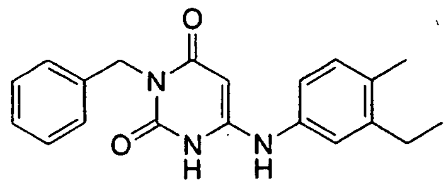
,

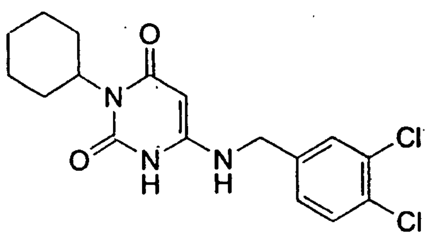


,

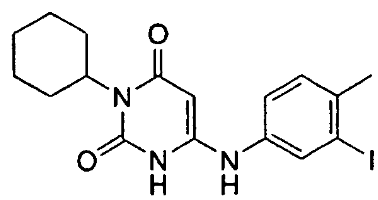
Table 1 Cont'd

,
,

,
,

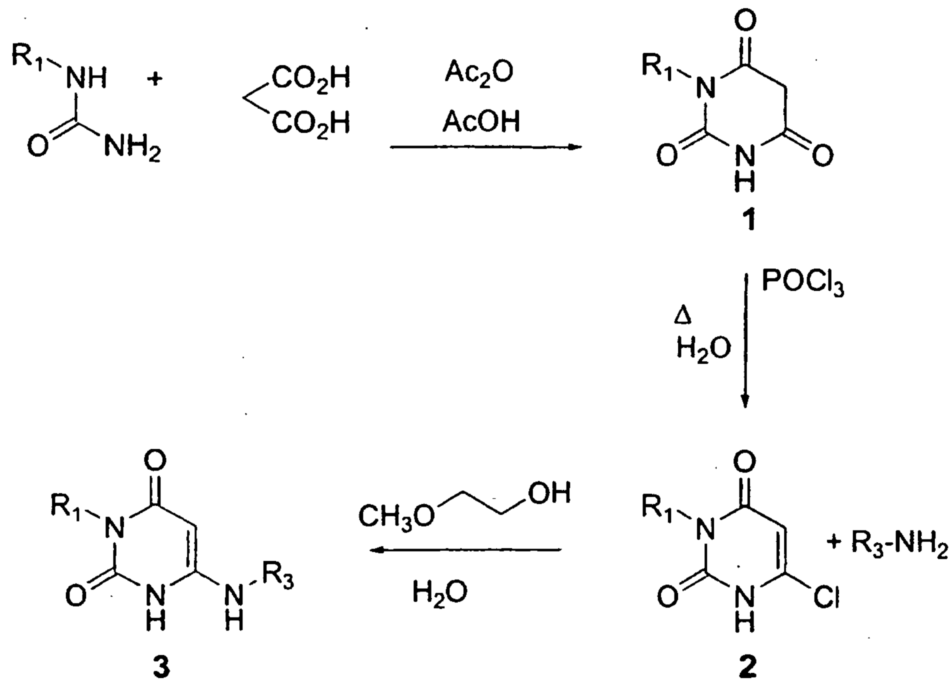


and

.

The process is illustrated using the general conditions shown in the accompanying flow chart.

Flow Chart A:



With reference to Flow Chart A above R_1 and R_2 are defined with respect to the compounds of Formula I. The compounds of the present invention wherein R_1 is ethyl and R_3 is 3-iodo-4-methyl phenyl, can be prepared by reacting ethylurea with malonic acid in the presence of acetic anhydride and acetic acid to give *N*-ethyl barbituric acid **1**. Further reaction with phosphorus oxychloride and water affords chloride **2** which is treated with the appropriately substituted amine using 2-methoxyethanol and water as the co-solvent to yield the desired compounds of Formula I.

The synthesis of the target compound is completed by removing any protecting groups which are present in the penultimate intermediate using standard techniques which are well known to those skilled in the art. The deprotected final product is then purified, as necessary, using standard techniques such as ion exchange chroma-tography, HPLC on reverse phase silica gel, MPLC on reverse phase polystyrene gel, and the like or by recrystallization.

The final product may be characterized structurally by standard techniques such as NMR, IR, MS, and UV. For ease of handling, the final product, if not crystalline, may be lyophilized from water to afford an amorphous, easily handled solid.

The compounds of the present invention are valuable antibacterial agents active against various Gram-positive and to a lesser extent Gram-negative bacteria, and accordingly find utility in human and veterinary medicine.

Many of compounds of the present invention are biologically active against MRSA/MRCNS. In vitro antibacterial activity is predictive of in vivo activity when the compounds are administered to a mammal infected with a susceptible bacterial organism.

Using standard susceptibility tests, the compounds of the invention are determined to be active against MRSA.

The compounds of the invention can be formulated in pharmaceutical compositions by combining the compound with a pharmaceutically acceptable carrier. Examples of such carriers are set forth below.

The compounds may be employed in powder or crystalline form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically, orally and parenterally by injection (intravenously or intramuscularly).

Compositions for injection, a preferred route of delivery, may be prepared in unit dosage form in ampules, or in multidose containers. The injectable compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain various formulating agents. Alternatively, the active ingredient may be in powder (lyophillized or non-lyophillized) form for reconstitution at the time of delivery with a suitable vehicle, such as sterile water. In injectable compositions, the carrier is typically comprised of sterile water, saline or another injectable liquid, e.g., peanut oil for intramuscular injections. Also, various buffering agents, preservatives and the like can be included.

Topical applications may be formulated in carriers such as hydrophobic or hydrophilic bases to form ointments, creams, lotions, in aqueous, oleaginous or alcoholic liquids to form paints or in dry diluents to form powders.

Oral compositions may take such forms as tablets, capsules, oral suspensions and oral solutions. The oral composions may utilize carriers such as conventional formulating agents, and may include sustained release properties as well as rapid delivery forms.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated, the route and frequency of administration, the sensitivity of the pathogen to the particular compound selected, the virulence of the infection and other factors. Such matters, however, are left to the routine discretion of the physician according to principles of treatment well known in the antibacterial arts. Another factor influencing the precise dosage regimen, apart from the nature of the infection and peculiar identity of the individual being treated, is the molecular weight of the compound.

The compositions for human delivery per unit dosage, whether liquid or solid, may contain from about 0.01% to as high as about 99% of active material, the preferred range being from about 10-60%. The composition will generally contain from about 15 mg to about 2.5 g of the active ingredient; however, in general, it is preferable to employ dosage amounts in the range of from about 250 mg to 1000 mg. In parenteral administration, the unit dosage will typically include the pure compound in sterile water solution or in the form of a soluble powder intended for solution, which can be adjusted to neutral pH and isotonic.

The invention described herein also includes a method of treating a bacterial infection in a mammal in need of such treatment comprising administering to said mammal a compound of formula I in an amount effective to treat said infection.

The preferred methods of administration of the Formula I antibacterial compounds include oral and parenteral, e.g., i.v. infusion, i.v. bolus and i.m. injection.

For adults, about 5-50 mg of Formula I antibacterial compound per kg of body weight given one to four times daily is preferred. The preferred dosage is 250 mg to 1000 mg of the antibacterial given one to four times per day. More specifically, for mild infections a dose of about 250 mg two or three times daily is recommended. For moderate infections against highly susceptible gram positive organisms a dose of about 500 mg three or four times daily is recommended. For severe, life-threatening infections against organisms at the upper limits of sensitivity to the antibiotic, a dose of about 1000-2000 mg three to four times daily may be recommended.

For children, a dose of about 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg is typically recommended.

The invention is further described in connection with the non-limiting examples below, wherein the concentration of solutions were carried out on a rotary evaporator under reduced pressure. Flash chromatography was carried out on silica gel (230-400 mesh). NMR spectra were obtained at ambient temperature in deuterated dimethyl sulfoxide unless otherwise indicated. Coupling constants (J) are in hertz (Hz). All temperatures given in the following examples are in degrees Celsius.

Abbreviations: diethyl ether (ether), room temperature (rt), hour(s) (h), minute(s) (min). "NMR," unless otherwise specified, refers to ^1H nuclear magnetic resonance spectroscopy and "TLC" refers to thin-layer SiO_2 chromatography. "MS" refers to mass spectroscopy and "HPLC" refers to high-pressure liquid chromatography.

MS CONDITIONS

MS A. Samples were run on a Finnigan TSQ700 by Flow Injection Electrospray Ionization MS. Mobile phase: 82% AcN with 1.3M TFA-NH_4 Formate.

MS B. Samples were run on a Finnigan SSQ710 by Flow Injection Particle Beam Election Impact Ionization MS. Mobile phase: 80:20 $MeOH:CH_2Cl_2$.

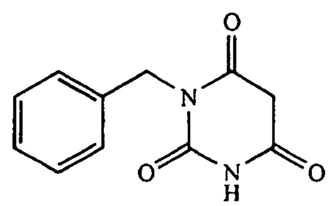
HPLC CONDITIONS

HPLC A. Retention time using the following conditions: Column: YMC ODS A, 5μ, 4.6 x 50 mm; Gradient Eluant: 10:90 to 90:10 v/v H_2O/CH_3CN + 0.5% TFA over 4.5 min, hold 30 sec; Detection: PDA, 210-400 nm; Flow Rate: 2.5 mL/min.

HPLC B. Retention time using the following conditions: Column: YMC ODS A, 5μ, 4.6 x 33 mm C18; Gradient Eluant: 10:90 to 90:10 v/v H_2O/CH_3CN + 0.5% TFA over 4.5 min, hold 30 sec; Detection: PDA, 210-400 nm; Flow Rate: 2.5 mL/min.

EXAMPLE 1

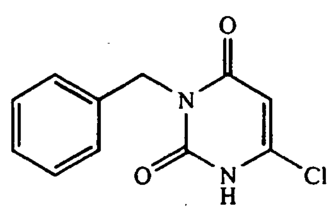
Step A: Preparation of 1



1

A mixture of benzylurea (2 g, 13.32 mmol), malonic acid (1.61 g, 15.45 mmol) and glacial acetic acid (5 mL) was stirred at 70° for 1 h. Acetic anhydride (3 mL) was added dropwise over 10 min and the reaction stirred at 90° for a further 2 h. The reaction was concentrated *in vacuo* and the resultant residue triturated with EtOH (20 mL). The product was collected by filtration and the solid washed with EtOH (2 x 5 mL) and dried (vacuum oven, 60°) to afford **1** as a white powder. HPLC C: 1.92 min.

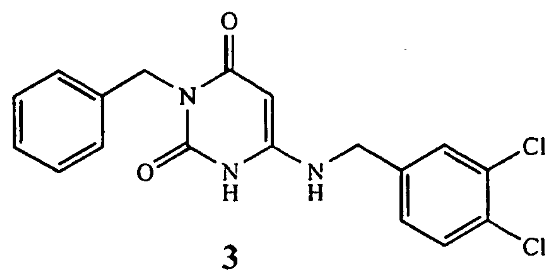
Step B: Preparation of 2



2

A mixture of *N*-benzylbarbituric acid **1** (1 g, 4.58 mmol) and phosphorus oxychloride (6 mL) was treated cautiously over 10 min with water (0.15 mL). The mixture was stirred at 135° for 1 h and the excess phosphorus oxychloride removed *in vacuo*. The remaining residue was poured into water (20 mL) and the crude product collected by filtration. Further purification by recrystallization from EtOH gave **2** as yellow powder. NMR: δ 5.08 (s, 2 H), 5.89 (s, 1 H), 7.28-7.47 (m, 5 H), 9.9 (bs, 1 H). HPLC C: 2.21 min.

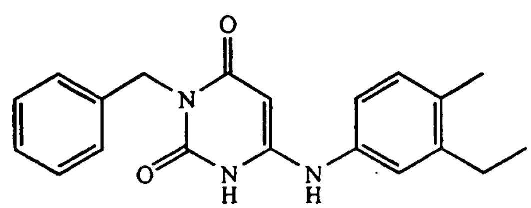
Step C: Preparation of 3



3

A mixture of 3-benzyl-6-chlorouracil **2** (50 mg, 0.21 mmol) and 3,4-dichlorobenzylamine (0.111 g, 0.63 mmol) in 2-methoxyethanol (3 mL) / H_2O (1 mL) was heated at reflux for 12 h. The reaction was diluted with H_2O (10 mL) and the product collected by filtration. The solid was washed with $CHCl_3$ (2 x 10 mL), dried (vacuum oven, 60°) and purified by chromatography on silica gel with EtOAC-hexane (1:39) to afford **3** as a white powder. NMR: δ 4.30 (d, *J* 6.2 Hz, 2 H), 4.6 (bs, 1 H), 4.82 (bs, 2 H), 6.74 (s, 1 H), 7.19-7.34 (m, 6 H), 7.59-7.64 (m, 2 H), 10.6 (s, 1 H). HPLC C: 3.17 min.

EXAMPLE 2

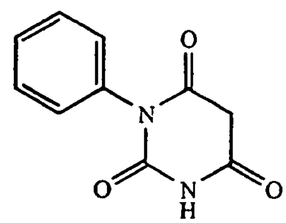


4

Using the procedure in Example 1, Step C 3-benzyl-6-chlorouracil **2** was reacted with 3-ethyl-4-methyl aniline [G. E. Wright *et al.*, *J. Med. Chem.*, **27**, 181-185 (1984)] to afford **4** as light yellow powder. NMR: δ 1.12 (t, *J* 7.6 Hz, 1 H), 2.22 (s, 3 H), 2.56 (q, *J* 7.6 Hz, 2 H), 4.75 (s, 1 H), 4.87 (s, 2 H), 7.93-7.39 (m, 8 H), 8.21 (bs, 1 H), 10.48 (bs, 1 H). HPLC A: 3.28 min.

EXAMPLE 3

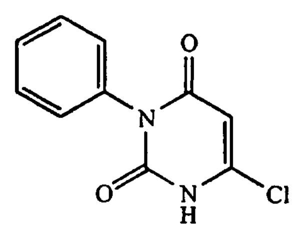
Step A:



5

Using the procedure in Example 1, Step A *N*-phenylurea was reacted with malonic acid to give *N*-phenylbarbituric acid **5**. NMR: δ 3.71 (s, 2 H), 7.07-7.51 (m, 5 H), 11.5 (bs, 1 H). HPLC C: 3.09 min.

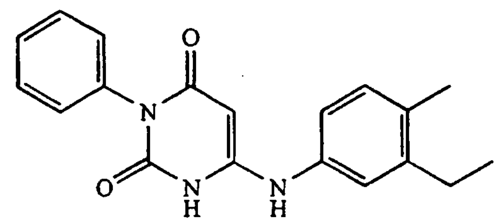
Step B:



6

Using the procedure in Example 1, Step B *N*-phenylbarbituric acid **5** was reacted with phosphorus oxychloride to give 3-phenyl-6-chlorouracil **6.** NMR: δ 5.99 (s, 1 H), 7.23-7.54 (m, 5 H), 8.46 (bs, 1 H). HPLC A: 1.89 min.

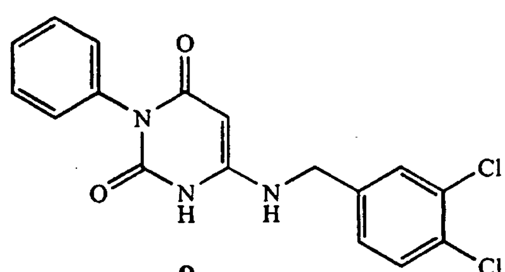
Step C:



7

Using the procedure in Example 1, Step C 3-phenyl-6-chlorouracil **6** was reacted with 3-ethyl-4-methyl aniline [G. E. Wright *et al.*, *J. Med. Chem.*, **27**, 181-185 (1984)] to afford **7** as light yellow powder. NMR: δ 1.15 (t, *J* 7.6 Hz, 1 H), 2.23 (s, 3 H), 2.58 (q, *J* 7.6 Hz, 2 H), 4.77 (s, 1 H), 7.01-7.41 (m, 8 H), 8.12 (bs, 1 H), 10.56 (bs, 1 H). HPLC C: 2.75 min.

EXAMPLE 4

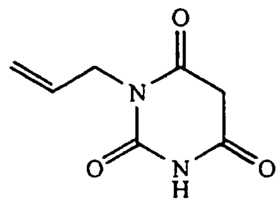


8

Using the procedure in Example 1, Step C 3-phenyl-6-chlorouracil **6** was reacted with 3,4-dichlorobenzylamine to afford **8** as a white powder. NMR: 4.32 (d, *J* 6.2 Hz, 2 H), 4.61 (bs, 1 H), 6.84 (bs, 1 H), 7.11-7.38 (m, 2 H), 7.35-7.40 (m, 4 H), 7.62-7.69 (m, 2 H). HPLC C: 2.67 min.

EXAMPLE 5

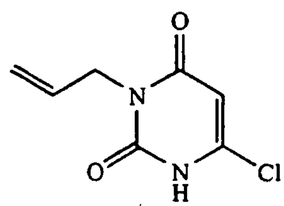
Step A:



9

Using the procedure in Example 1, Step A *N*-allylurea was reacted with malonic acid to give *N*-allylbarbituric acid **9**. NMR: δ 4.25 (m, 4 H), 5.05 (dd, *J* 10.2 and 1.7 Hz, 1 H), 5.15 (dd, *J* 17.2 and 1.7 Hz, 1 H), 5.84 (ddt, *J* 17.2, 10.2 and 1.7 Hz, 1 H), 11.4 (bs, 1 H).

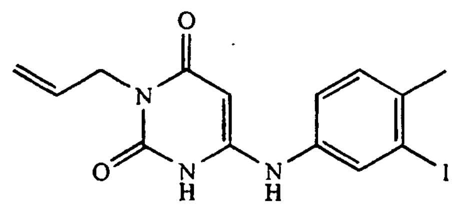
Step B:



10

Using the procedure in Example 1, Step B *N*-allylbarbituric acid **9** was reacted with phosphorus oxychloride to give 3-allyl-6-chlorouracil **10**. NMR: δ 4.25 (m, 2 H), 5.06 (m, 2 H), 5.85 (m, 1 H), 5.98 (s, 1 H), 12.38 (bs, 1 H). HPLC A: 1.17 min.

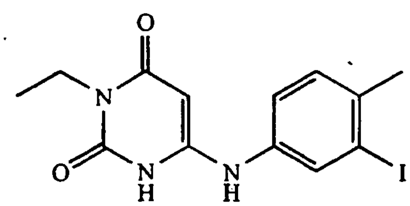
Step C:



11

Using the procedure in Example 1, Step C 3-allyl-6-chlorouracil **10** was reacted with 3-iodo-4-methyl aniline to afford **11** as a light yellow powder. NMR: δ 2.33 (s, 3 H), 4.27 (d, *J* 5.2 Hz, 2 H), 4.74 (s, 1 H), 5.00-5.06 (m, 2 H), 5.74 (m, 1 H), 7.14 (dd, *J* 8.2 and 2.1 Hz, 1 H), 7.31 (d, *J* 8.5 Hz, 1 H), 7.63 (d, *J* 2.1 Hz, 1 H), 8.28 (bs, 1 H), 10.6 (bs, 1 H). HPLC C: 2.61 min.

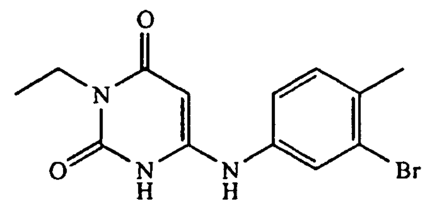
EXAMPLE 6



12

A mixture of 3-ethyl-6-chlorouracil (100 mg, 0.57 mmol) [N. C. Brown *et al.*, *J. Med. Chem.*, **42**, 2035-2040 (1999)] and 3-iodo-4-methylaniline (0.267 g, 1.80 mmol) in 2-methoxyethanol (6 mL) / H_2O (2 mL) was heated at reflux for 6 h. The reaction was diluted with H_2O (10 mL) and the product collected by filtration. The solid was washed with hot $CHCl_3$ (2 x 10 mL) and dried (vacuum oven, 60°) to afford **12** as a white powder. NMR: δ 1.04 (t, *J* 6.9 Hz, 3 H), 2.32 (s, 3 H), 3.69 (q, *J* 6.9 Hz, 2 H), 4.73 (s, 1 H), 7.16 (m, 1 H), 7.30 (d, *J* 8.2 Hz, 1 H), 7.62 (bs, 1 H), 8.24 (bs, 1 H), 10.6 (bs, 1 H). HPLC A: 2.61 min.

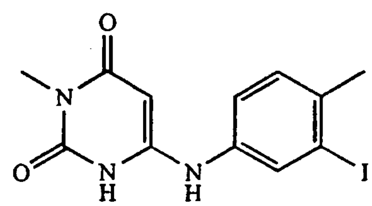
EXAMPLE 7



13

A mixture of 3-ethyl-6-chlorouracil (100 mg, 0.57 mmol) [N. C. Brown *et al.*, *J. Med. Chem.*, **42**, 2035-2040 (1999)] and 3-bromo-4-methylaniline (0.267 g, 1.15 mmol) in 2-methoxyethanol (6 mL) / H_2O (2 mL) was heated at reflux for 6 h. The reaction was diluted with H_2O (10 mL) and the product collected by filtration. The solid was washed with hot $CHCl_3$ (2 x 10 mL) and dried (vacuum oven, 60°) to give **13** as a white powder. NMR: δ 1.03 (t, *J* 6.9 Hz, 3 H), 2.31 (s, 3 H), 3.67 (q, *J* 6.9 Hz, 2 H), 4.71 (s, 1 H), 7.14 (m, 1 H), 7.33 (d, *J* 8.3 Hz, 1 H), 7.4 (bs, 1 H), 8.29 (bs, 1 H), 10.57 (bs, 1 H).

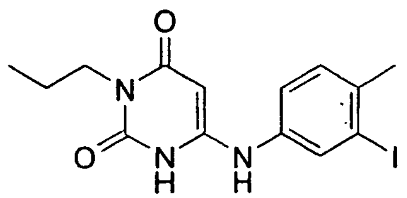
EXAMPLE 8



14

A mixture of 3-methyl-6-chlorouracil (40 mg, 0.25 mmole) [N. C. Brown *et al.*, *J. Med. Chem.*, **42**, 2035-2040 (1999)] and 3-iodo-4-methylaniline (0.174 g, 0.75 mmol) in 2-methoxyethanol (3 mL) / H_2O (1 mL) was heated at reflux for 12 h. The reaction was diluted with H_2O (10 mL) and the product collected by filtration. The solid was washed with hot $CHCl_3$ (2 x 10 mL) and dried (vacuum oven, 60°) to give **14** as a white powder. NMR: δ 2.32 (s, 3 H), 3.05 (s, 3 H), 4.74 (s, 1 H), 7.15 (m, 1 H), 7.31 (d, *J* 8.2 Hz, 1 H), 7.4 (s, 1 H), 8.26 (bs, 1 H), 10.61 (bs, 1 H). HPLC C: 2.37 min.

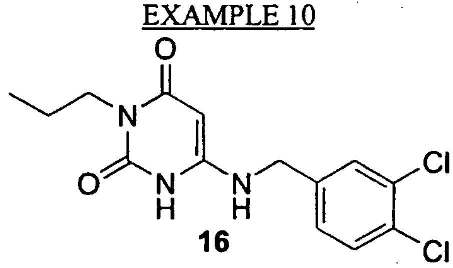
EXAMPLE 9



15

A mixture of 3-propyl-6-chlorouracil (25 mg, 0.13 mmol) [N. C. Brown *et al.*, *J. Med. Chem.*, **42**, 2035-2040 (1999)] and 3-iodo-4-methylaniline (47 mg, 0.20 mmol) [G. E. Wright *et al.*, *J. Med. Chem.*, **27**, 181-185 (1984)] in 2-methoxyethanol (3 mL) / H_2O (1 mL) was heated at reflux for 12 h. The reaction was diluted with H_2O (10 mL) and the product collected by filtration. The solid was washed with hot $CHCl_3$ (2 x 10 mL) and dried (vacuum oven, 60°) to give **15** as a white powder. NMR: δ 0.81 (t, *J* 7.3 Hz, 3 H), 1.48 (m, 2 H), 2.31 (s, 3 H), 3.65 (t, *J* 7.3 Hz, 2 H), 4.72 (s, 1 H), 7.12 (m, 1 H), 7.31 (d, *J* 8.0 Hz, 1 H), 7.63 (s, 1 H), 8.18 (bs, 1 H), 10.6 (bs, 1 H). HPLC A: 2.75 min.

EXAMPLE 10

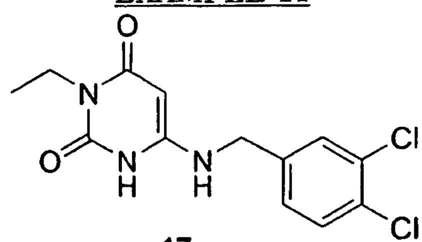


16

A mixture of 3-propyl-6-chlorouracil (25 mg, 0.13 mmol) [N. C. Brown *et al.*, *J. Med. Chem.*, **42**, 2035-2040 (1999)] and 3,4-dichlorobenzylamine (69 mg, 0.39 mmol) in 2-methoxyethanol (1.5 mL) / H_2O (0.5 mL) was heated at reflux for 12 h. The reaction was diluted with H_2O (10 mL) and the product collected by filtration. The solid was washed with hot $CHCl_3$ (2 x 10 mL) and dried (vacuum oven, 60°) to give **16** as a white powder. NMR: δ 0.78 (t, *J* 7.3 Hz, 3 H), 1.44 (q, *J* 7.3 Hz, 2 H), 3.58 (t, *J* 7.3 Hz, 2 H), 4.28 (d, *J* 5.9 Hz, 2 H), 4.56 (s, 1 H), 6.66 (m, 1 H), 7.31

(d, J 8.0 Hz, 1 H), 7.57 (s, 1 H), 7.59 (d, J 8.0 Hz, 1 H), 10.21 (bs, 1 H). HPLC C: 2.59 min.

EXAMPLE 11

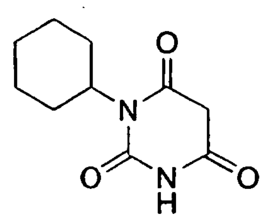


17

A mixture of 3-ethyl-6-chlorouracil (100 mg, 0.57 mmol) [N. C. Brown *et al.*, *J. Med. Chem.*, **42**, 2035-2040 (1999)] and 3,4-dichlorobenzylamine (0.324 g, 1.84 mmol) in 2-methoxyethanol (6 mL) / H_2O (2 mL) was heated at reflux for 6 h. The reaction was diluted with H_2O (10 mL) and the product collected by filtration. The solid was washed with hot $CHCl_3$ (2 x 10 mL) and dried (vacuum oven, 60°) to afford **17** as a white powder. NMR ($CDCl_3$): δ 1.00 (t, J 7.0 Hz, 3 H), 3.69 (q, J 7.0 Hz, 2 H), 4.26 (d, J 6.2 Hz, 2 H), 4.45 (s, 1 H), 6.69 (m, 1 H), 7.30 (dd, J 8.2 and 2.1 Hz, 1 H), 7.57 (d, J 1.8 Hz, 1 H), 7.61 (d, J 8.2 Hz, 1 H), 8.24 (bs, 1 H), 10.28 (bs, 1 H).

EXAMPLE 12

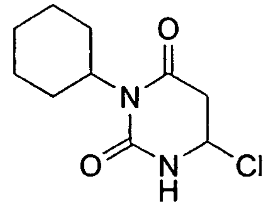
Step A:



18

Using the procedure in Example 1, Step A *N*-cyclohexylurea was reacted with malonic acid to give *N*-cyclohexylbarbituric acid **18**. NMR: δ 1.03-1.13 (m, 1 H), 1.18-1.29 (m, 2 H), 1.52-1.62 (m, 3 H), 1.71-1.78 (m, 2 H), 2.07-2.17 (m, 2 H), 3.56 (s, 1 H), 4.36-4.44 (m, 1 H), 11.17 (s, 1 H).

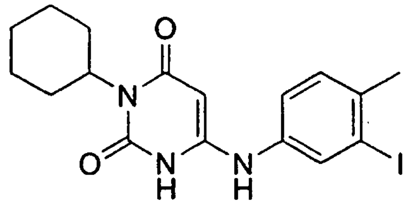
Step B:



19

Using the procedure in Example 1, Step B *N*-cyclohexylbarbituric acid **19** was reacted with phosphorus oxychloride to give 3-cyclohexyl-6-chlorouracil **19**. NMR: δ 1.03-1.13 (m, 1 H), 1.18-1.29 (m, 2 H), 1.46-1.52 (m, 2 H), 1.55-1.62 (m, 1 H), 1.71-1.78 (m, 2 H), 2.19-2.28 (m, 2 H), 4.49-4.56 (m, 1 H), 5.8 (s, 1 H), 12.2 (bs, 1 H). HPLC C: 1.81 min.

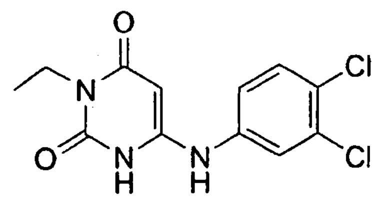
Step C:



20

Using the procedure in Example 1, Step C 3-cyclohexyl-6-chlorouracil **20** was reacted with 3-iodo-4-methyl aniline to afford **20** as a light tan powder. NMR: δ 1.03-1.13 (m, 1 H), 1.18-1.29 (m, 2 H), 1.42-1.48 (m, 2 H), 1.55-1.61 (m, 1 H), 1.71-1.77 (m, 2 H), 2.23-2.32 (m, 2 H), 2.32 (s, 3 H), 4.51-4.58 (m, 1 H), 4.69 (s, 1 H), 7.14 (dd, *J* 8.15 and 2.3 Hz, 1 H), 7.29 (d, *J* 8.1 Hz, 1 H), 7.61 (d, *J* 2.3 Hz, 1 H), 8.16 (s, 1 H), 10.4 (bs, 1 H). HPLC A: 3.31 min.

EXAMPLE 13



21

Using the procedure in Example 1, Step C 3-cyclohexyl-6-chlorouracil 20 was reacted with 3,4-dichlorobenzylamine to afford 21 as a yellow powder. NMR: δ 1.0-1.1 (m, 1 H), 1.15-1.28 (m, 2 H), 1.37-1.43 (m, 2 H), 1.55-1.59 (m, 1 H), 1.68-1.74 (m, 2 H), 2.2-2.29 (m, 2 H), 4.26 (d, *J* 6.2 Hz, 2 H), 4.46 (s, 1 H), 4.46-4.54 (m, 1 H), 6.61 (bm, 1 H), 7.29 (dd, *J* 8.2 and 1.8 Hz, 1 H), 7.58 (d, *J* 1.8 Hz, 1 H), 7.6 (d, *J* 8.2 Hz, 1 H), 10.3 (bs, 1 H). HPLC C: 3.12min.

Biological Assays

Cloning, Expression, and Purification

DNA polymerase III (Pol III) was cloned by PCR from S. aureus genomic DNA. The Pol III gene was cloned into pET15. Pol III/pET15 was transformed into BL21 cells. The cells were grown at 29°C in M9ZB media containing ampicillin and chloramphenicol to an OD of 1.0. The cells were induced by adding 1 mM IPTG and grown for three hours. The cells were centrifuged at 2500 x g for 10 minutes. The cell pellet was resuspended in 50 mM Tris, pH 7.4, 0.1% Triton X100, 1 mM EDTA, 20% glycerol, and complete protease inhibitor cocktail (Boehringer Mannheim) and lysed by freeze/thawing three times in a dry ice and methanol bath. The lysate was centrifuged at 10,000 x g for one hour.
The supernatant was loaded onto a HiTrapQ column that was equilibrated in 50 mM Tris, pH 7.4, 20% glycerol, and 1 mM EDTA. Following loading, the column was washed with 20 column volumes of buffer. The Pol III was eluted using a linear NaCl gradient from 0-0.5 M. The Pol III activity eluted between 0.3 and 0.4 M NaCl. The peak of activity was loaded onto a HiTrap Blue column equilibrated in 50 mM Tris, Ph 7.4, 20% glycerol, 1mM EDTA, and 1 mg/ml BSA. The column was washed with 10 column volumes of equilibration buffer, followed by a wash with 20 column

volumes of equilibration buffer containing 0.5 M NaCl. The Pol III was eluted by washing the column with equilibration buffer containing 3 M NaCl.

Inhibition Assay

The reaction mix consisted of 30 mM Tris HCl, pH 7.5, 20% glycerol, 4 mM DTT, 10 mM MgOAc, 0.003 mM dATP, 0.003 mM dGTP, 0.001 mM dCTP, 0.001 mM ^{3}H-dTTP, and 0.35 mg/ml 'activated' calf thymus DNA (Worthington Enzymes) in a final volume of 0.1 ml. The assay was initiated by the addition of enzyme and incubated for 30 minutes at 30°C. The assay was stopped by the addition of cold 10%TCA/0.1% NaPPi. The incorporation of ^{3}H-dTTP into the calf thymus DNA was monitored by capturing the precipitated DNA onto a GF/C filter; followed by counting in a scintillation counter. The range of activity for the compounds of Formulas I and II in this assay were about 2 to about 25 μM.

PICA (**DNA Polymerase III Inhibition Whole-Cell-based Assay**) Standard Operating Procedures

Assay organism growth and storage conditions:

Five organisms were tested in the PICA assay. Specific conditions for the growth and storage of these cultures are provided in the table below. Standard microbiological techniques were used in the routine maintenance of the cultures.

Strain	Species	Long term storage	Working slant	Media Overnight broth	MIC assay	Purity plate	Inoculum Dilution
F2	*B. subtilis*	LB slant room temp	LB	LB	LB	LB	1 to 100
MB4926[1]	*E. coli envA*	Frozen vial TSB	BHI	TSB	MH	LB & LB+ rif[1]	1 to 100
RLA-1	*E. faecium*	Frozen vial BHI	BHI	TSB	BHI	BHI	1 to 10
MB2865	*S. aureus*	Frozen slant TSB	Thawed slant TSB	TSB	MH	BHI	1 to 100
MCL5350	*S. pneumoniae*	Frozen slant BHI+10%HS	Thawed slant BHI+10%HS	TSB+ 10%HS	BHI	Blood Agar	1 to 10

[1] This strain was replaced at the end of the program by a more sensitive strain (MB5746).

MLC assay:

Samples from were tested initially in three concentrations, 100 μM, 10 μM, and 1 μM final. Samples were resuspended at a concentration of 2 or 10 mM in DMSO (if required), then serial 10-fold dilutions of this stock were prepared to achieve the final concentrations indicated. Samples were diluted either by hand or using a Denley Wellpro liquid handling system (manufactured by Labsystems). Five μl of each concentration were transferred from the dilution plate to replica assay plates either by hand or using a Quadra-96 model 320 liquid handling device (manufactured by Tomtec). Media was added either by hand or using the Denley to a final assay volume of 100 μl to give a final DMSO concentration of 5%. DMSO was run as the vehicle control. Media used were specific for each strain as indicated in the table above. Assay plates were inoculated using an MIC-2000 (manufactured by Dynex Technologies) from cultures diluted into phosphate-buffered saline (made by Gibco-BRL)as indicated in the table above. Assay plates were incubated overnight at 37°C and then examined for the presence/absence of growth of the bacteria in the wells.

Results are expressed as the MLC, that is, the minimum log concentration that gives inhibition of the growth of the indicated organism (ie >100, 100, 10, and ≤1). Any sample which was active on one or more strains was then tested in a more shallow dilution series to give a more specific measure of activity (see MIC below). The range of activity for the compounds of Formulas I and II in this assay were about 10 to about 100 μM.

MIC assay:

The procedures for the MIC assay were essentially as described above for the MLC assay, except that serial two-fold dilutions of the compounds were made from a final initial high concentration of 100 μM. In addition, the effect of serum albumin on the activity of the compounds was examined by testing MICs against the MB2865 strain in the presence and absence of a final 4.3 mg/ml concentration of human serum fraction V (Calbiochem). Results are expressed as the minimum

inhibitory concentration (MIC); the lowest two-fold dilution which gives inhibition of growth (>100, 100, 50, 25, 12.5 etc., in μM). The range of activity for the compounds of Formulas I and II in this assay were about <0.5 to about 50 μM.

MOA assay:

Compounds which were active in the MIC assay were tested for the mode of action (MOA) by whole-cell dose-response labeling. Each compound was tested versus five different labeled precursors to investigate the effect on DNA synthesis (6- ^{3}H Thymidine, 1 μCi/ml final, plus uridine at 50 μg/ml final concentration), RNA synthesis (5,6- ^{3}H Uracil, 1 μCi/ml final), protein synthesis (4,5- ^{3}H Leucine, 5 μCi/ml final), phospholipid synthesis (2-^{3}H Glycerol, 1 μCi/ml final), and cell wall synthesis (2,3- ^{3}H-alanine, 5 μCi/ml final, plus chloramphenicol at 100 μg/ml final). All labeled precursors were either from Amersham or New England Nuclear. In most cases MB2865 was the assay organism, but in cases where compounds had activity against the Bacillus strain and not MB2865, then that strain was used. Overnight cultures grown in Muller-Hinton medium were diluted 1:100 (3 ml) into 300 ml (pre-warmed) MH broth containing 50 μg/ml uridine,. incubated at 37°C with shaking to an OD of 0.1 (mid-log), and harvested by centrifugation. The cells were resuspended to an OD of 0.5 in pre-warmed MH medium.

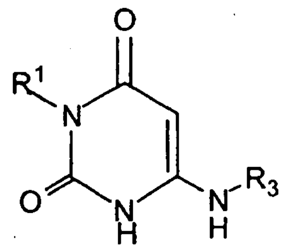
Test and control compounds were serially diluted either two-fold or three-fold (depending on potency) in the appropriate diluent for the compound (water or DMSO) and then 5 μl of each transferred to each of five assay plates. A final assay volume of 100 μl also included precursor diluted into MH medium to obtain the final concentration indicated above and 70 μl of cells at OD 0.5. Addition of cells began the reaction allowed to proceed for 20 min. and stopped by addition of 50% TCA to a final concentration of 10%. TCA precipitable counts were collected onto glass fiber filters (Wallac) using a Skatron Micro96 harvester. Filter mats were placed in bags with 10 ml scintillation fluid and loaded into cassettes for measurement in an LKB 1205 Betaplate counter (Wallac).

Results are expressed as the percentage of control counts (vehicle alone, no drug) present in each sample well plotted as a function of percent of control versus concentration of compound on a semi-log plot. The concentration of compound giving 50% inhibition of each macromolecular synthesis (IC_{50}) is

determined from this plot. The range of activity for the compounds of Formulas I and II in this assay were about 1.0 to about 25 μM.

WHAT IS CLAIMED IS:

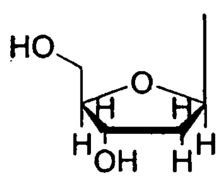
1. A compound represented by formula I:



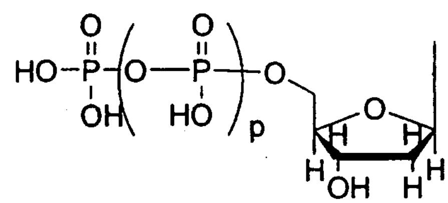
I

including pharmaceutically acceptable salts, stereoisomers or esters thereof, wherein:

R^1 represents H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $(CH_2)_nC_{3-10}$ alicyclic, $(CH_2)_nC_{3-10}$ heterocyclic, $(CH_2)_nC_{5-10}$ aryl, $(CH_2)_nC_{5-10}$heteroaryl, $(CH_2)_n$diaryl, $(CH_2)_nOR^2$, $(CH_2)_mCO_2R^2$, $(CH_2)_nN(R^2)_2$, $(CH_2)_nCON(R^2)_2$,



, or



;

said alkyl, alkenyl, alkynyl, aryl, heteroaryl, optionally substituted with 1 to 3 groups of R^a; and providing that when R^1 is H, CH_3, CH_2CH_3, $CH_2CH=CH_2$ or $(CH_2)_{2-5}CH_3$, R3 cannot be 3,4-trimethyleneanilino or when R^1 is H, CH_3, CH_2CH_3, $CH_2CH=CH_2$ or $(CH_2)_{2-5}CH_3$, R3 cannot be 3-ethyl-4-methylanilino;

m is 0 to 5; n is 0 to 5; p is 0 to 2;

R^2 represents H, C_{1-10} alkyl;

R^3 is C_{3-10}alicyclic, C_{3-10}heterocyclic, $(CH_2)_nC_{5-10}$aryl, $(CH_2)_nC_{5-10}$ heteroaryl, $NH(CH_2)_nC_{5-10}$aryl, or $NH(CH_2)_nC_{5-10}$heteroaryl, said aryl or heteroaryl optionally substituted with 1 to 3 groups of R;

R is H, C_{1-6} alkyl, C_{1-6} alkyl-OH, halo, C_{1-6} alkylhalo, OR^2, CN, CF_3, $N(R^2)_2$, CO_2R^2, NO_2, $NHCOR^2$, SO_2R^2 or SR^2;

R^a represents C_{1-10} alkyl, C_{3-8} cycloalkyl, halo, C_{1-6} alkyl-OH, OH, C_{1-6} alkylhalo, CF_3, NH_2, C_{1-6} alkylNH_2, -SH, -SC_{1-4}alkyl, -CN, -COC_{1-8}alkyl, -C_{5-10} aryl, -COC_{5-10} aryl, -C_{5-10} heteroaryl, -COC_{5-10} heteroaryl, C_{1-4}alkyl-aryl, $CONR^6R^7$, $NHCOR^2$, $OCOR^6$, -$NR^6(CO)R^7$, $NR^6(CO)NHR^7$, $NHSO_2R^6$, OR^6, CO_2R^6, or NR^6R^7 and

R^6 & R^7 independently represent H, C_{1-8} alkyl, C_{3-8} cycloalkyl, or -C_{5-10} aryl.

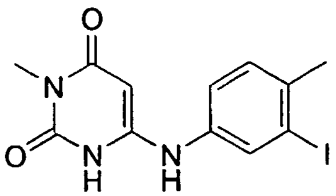
2. A compound in accordance with claim 1 wherein R^1 represents C_{1-8} alkyl, C_{2-8} alkenyl, $(CH_2)_nC_{5-10}$ aryl, or $(CH_2)_nC_{5-10}$ alicyclic, said alkyl, alkenyl, aryl or alicyclic optionally substituted with 1-3 groups of R^a.

3. A compound in accordance with claim 1 wherein R^3 C_{3-10}alicyclic, $(CH_2)_nC_{5-10}$aryl, $(CH_2)_nC_{5-10}$heteroaryl, or $NH(CH_2)_nC_{5-10}$aryl, said aryl or heteroaryl optionally substituted with 1 to 3 groups of R.

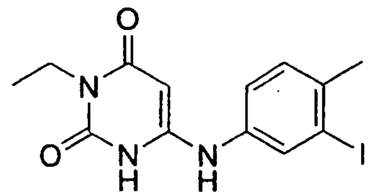
4. A compound in accordance with claim 1 wherein where R^1 represents C_{1-8} alkyl, C_{2-8} alkenyl, $(CH_2)_nC_{5-10}$ aryl, or $(CH_2)_nC_{5-10}$ alicyclic, said alkyl, alkenyl, aryl or alicyclic optionally substituted with 1-3 groups of R^a; and R^3 represents C_{3-10}alicyclic, $(CH_2)_nC_{5-10}$aryl, $(CH_2)_nC_{5-10}$heteroaryl, or $NH(CH_2)_nC_{5-10}$aryl, said aryl or heteroaryl optionally substituted with 1 to 3 groups of R, optionally substituted with 1 to 3 groups of R.

5. A compound in accordance with claim 1 which is represented in Table 1:

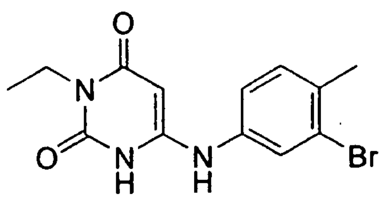
TABLE 1



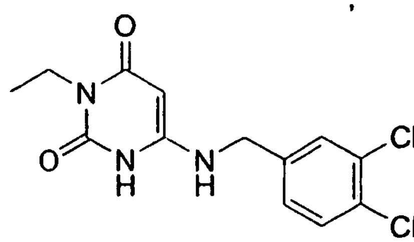
,



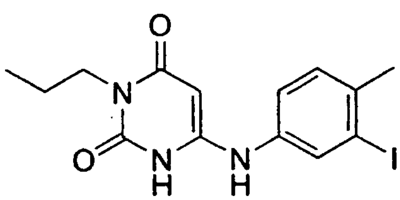
,



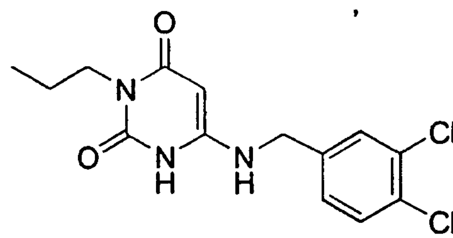
,



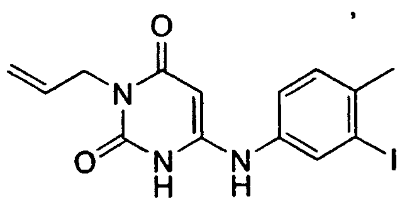
,



,

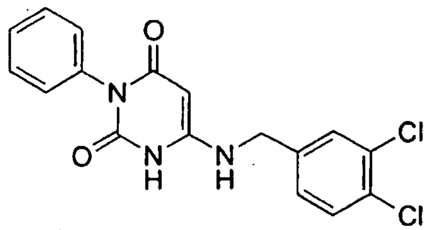
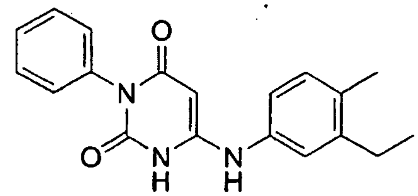


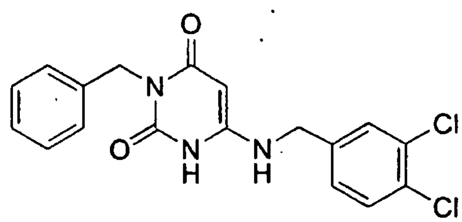
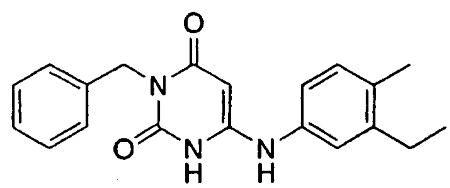
,

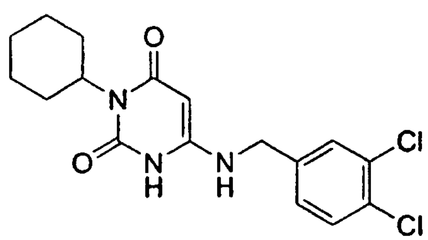
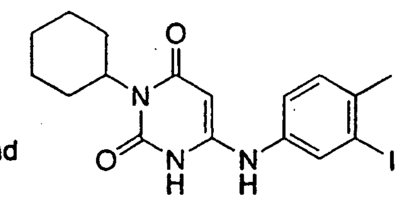


,

Table 1 Cont'd

,
,

,
,

 and .

6. A pharmaceutical composition comprised of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

7. A method of treating a bacterial infection comprising administering to a mammalian patient in need of such treatment a compound as defined in claim 1 in an amount which is effective for treating a bacterial infection.

8. A method of treating a bacterial infection involving methicillin resistant Staphylococcus aureus, methicillin resistant Staphylococcus epidermidis, B. subtilis, Enterococcus facalis/fecium, Streptococcus pneumoniae, methicillin resistant coagulase negative Staphylococci microoganisms or any combination thereof comprising administering to a mammalian patient in need of such treatment a

compound as defined in claim 1 in an amount which is effective for treating a bacterial infection.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/28809

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 239/545; A61K 31/513
US CL : 544/312; 514/269, 274
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/312; 514/269, 274

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/06614 A1 (UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER) 07 March 1996 (07.03.1996), see page 4, first formula and the compounds on pages 5-6.	1-4, 6-8
X	US 2,980,665 A (LANGLEY) 18 April 1961 (18.04.1961), see the intermediates in Examples 1 and 14.	1, 3, 6
X	US 3,238,208 A (GERNS et al) 01 March 1966 (01.03.1966), see the compounds of formula I and species in the Table in col. 2.	1, 3, 6
X	Chem. abstr., Vol. 131, No. 8, 23 August 1999 (Columbus, OH, USA), page 399, column 2, the abstract No. 99748h, TARANTINO, P.M.Jr. '6-Anilinouracil-Based Inhibitors of Bacillus subtilis DNA Polymerase III.' J. Med. Chem. 1999, 42(11), 2035-2040 (Eng), see entire document.	1-4, 6-8
X	TARANTINO, P.M.Jr. Inhibitors of DNA Polymerase III as Novel Antimicrobial Agents against Gram-Positive Eubacteria. Antimicrobial Agents and Chemotherapy, August 1999, Vol. 43, No. 8, pages 1982-1987, especially page 1984.	1-4, 6-8
X	TRANTOLO, D.J. Inhibitors of Bacillus subtilis DNA Polymerase III. J. Med. Chem. 1986, Vol. 29, No. 5, pages 676-681, see entire document.	1-4, 6-8

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search 07 February 2001 (07.02.2001)	Date of mailing of the international search report 30 MAR 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Deepak Rao TERRY J. DEY PARALEGAL SPECIALIST TECHNOLOGY CENTER 1600 Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/28809

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. abstr., Vol. 92, No. 15, 14 April 1980 (Columbus, OH, USA), page 269, column 2, the abstract No. 123967c, WRIGHT, G.E. 'Butylanilinouracil: a selective inhibitor of HeLa cell DNA synthesis.' Nucleic Acids Res. 1980, 8(1), 99-109 (Eng), see entire document.	1, 3, 6-8
X	Chem. abstr., Vol. 71, No. 17, 27 October 1969 (Columbus, OH, USA), page 37, column 1, the abstract No. 77587v, PREUSSEL, B. 'Differential inhibitor sensitivities of thymidine phosphorylases.' Biochem. Pharmacol. 1969, 18(8), 2035-8 (Eng), see entire document.	1, 3, 6-8
X	Chem. abstr. Vol. 72, No. 9, 02 March 1970 (Columbus, OH, USA), page 452, column 2, the abstract No. 43593z, BAKER, B.R. 'Irrefersible enzyme inhibitors.' J. Med. Chem. 1970, 13(1), 87-9 (Eng), see entire document.	1, 3, 6-8

Form PCT/ISA/210 (continuation of second sheet) (July 1998)